Evaluation of the predictive potential of the short acute retroviral syndrome severity score for HIV-1 disease progression in individuals with acute HIV infection

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Evaluation of the Predictive Potential of the Short Acute Retroviral Syndrome Severity Score for HIV-1 Disease Progression in Individuals With Acute HIV Infection

To the Editors:

Expert guidelines now recommend immediate antiretroviral therapy (ART) for all HIV-infected persons regardless of CD4 cell count, to reduce the risk of disease progression and prevent HIV transmission.[1,2] There is also increasing evidence that very early ART benefits the individual infected with HIV by leading to more rapid and robust immunologic recovery, lower inflammation, and reduced viral reservoir size compared with a later start.[3–12] However, in low-income and middle-income countries, universal immediate ART is rarely available. To assist clinicians in regions where universal ART is not available in prioritizing provision of immediate ART to patients who benefit most, Braun et al recently developed the Acute Retroviral Syndrome (ARS) Severity Score (ARSSS). Following the hypothesis that severity of primary HIV infection correlates with disease progression,[13–17] the score includes mostly clinical variables that reflect the intensity of the clinical presentation of primary HIV infection.[18] The score was evaluated retrospectively among 290 individuals of the Zurich primary HIV infection study and correlated well with validated surrogate markers associated with HIV-1 disease progression, that is, baseline $CD4^+$ cell count, baseline viral load, and set-point viral load.[18] External validation of the ARSSS is still missing, however. Furthermore, it remains unclear if the score has predictive validity also in individuals at the earliest stage of HIV infection, as only 3 of these 290 individuals fulfilled the earliest criteria of acute HIV infection (AHI; ie, Fiebig I or II).[18,19]

In this retrospective analysis of a prospective observational cohort study, we evaluated the performance of the ARSSS[18] in patients diagnosed with AHI between 2007 and 2014 by the San Diego Primary HIV Infection Consortium.[20] A total of 90 persons were identified with AHI and provided questionnaire responses on signs and symptoms of ARS at the time of AHI diagnosis, although only the subset of 48 individuals who provided information on whether they had sought medical attention for signs or symptoms of ARS (ie, a substantial 3-point component of the ARSSS) were included in this analysis (the question was not included in the questionnaire used between 2010 and 2012). All individuals were diagnosed with AHI with the "Early Test" that included routine individual donation (ID), HIV nucleic acid amplification testing (ID-NAT) to all rapid antibody-negative participants.[21–26] AHI was defined as having a negative or indeterminate HIV antibody test result with a positive ID-NAT, corresponding to Fiebig stages I–II, and a mean estimated duration of infection of 10 days.[19] At each participant's first visit after documentation of AHI diagnosis (median 4 days, interquartile range , 3–6 days after AHI testing), blood samples were collected for CD4 and viral load testing. Detailed information related to occurrence, duration, and start and stop dates for signs and symptoms associated with AHI were also collected.[27,28] Participants were asked if they had sought medical attention for any of these signs or any symptoms. In persons who reported symptoms that were ongoing, the date on which symptoms resolved as well as additional signs or symptoms occurring within 4 weeks after the AHI test were collected during follow-up.[20] The viral set point was defined as the first HIV-RNA measurement $\geq$90 days after the estimated date of infection in treatment-naive patients.[18]

We evaluated 2 versions of the ARSSS, the complete 6 variable[27] ARSSS assessment (ARSSS-full) in a subset of 19 participants and a shorted version (ARSSS-short) consisting of 4 variables in all 48 participants (Table 1).

For this evaluation, one of the originally proposed variables, "inpatient treatment" (ie, 3 points in ARSSS), was replaced by "seeking medical attention because of signs and symptoms of ARS," as inpatient treatment was not assessed in our cohort undergoing community-based testing. The other 3 variables of the ARSSS-short, namely presence of severe neurologic symptoms (eg, encephalitis, meningitis; 3 points), age $\geq$50 years (1 point), and fever (self-reported or documented $\geq$38°C; 1 point) remained unchanged and were assessed at the first visit after AHI diagnosis in all 48 individuals.

The ARSSS-full consisting of all 6 variables was assessed in the subset of 19/48 (40%) of participants who had safety laboratory results available (ie, those who initiated ART immediately after AHI diagnosis; laboratory results were always obtained before ART start).

For statistical analysis, SPSS version 23 (SPSS, Inc., Chicago, IL) was used. Correlation between ARSSS-short and ARSSS-full and viral loads, CD4/CD8 cell ratios, set-point viral loads and number, and duration of symptoms of

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TABLE 1. Short Version and Full Version of the ARSS Score, Demographics, and Clinical Characteristics of the Study Population and Comparison of Subcohorts With Short ARSSS >2 and ≤2

Scores	Variables	Individuals Fulfilling Variables of the Score, n (%)
Short ARSS score (maximum value 8 points)	(1) Seeking medical attention because of signs and symptoms of ARS (3 points)*	12/48 (25)
	(2) Presence of severe neurologic symptoms (3 points)	1/48 (2)
	(3) Age ≥ 50 yrs (1 point)	4/48 (8)
	(4) Fever (self-reported or documented ≥38°C; 1 point)	30/48 (63)
Full ARSS score (maximum value 10 points)	All variables of the short ARSS score PLUS	
	(5) Elevated liver enzymes (AST and/or ALT ≥30 U/l; 1 point)	6/19 (32)
	(6) Thrombocytopenia (platelet count <150 G/L; 1 point)	2/19 (11)

Demographics	Study Cohort	Subcohort With ARSSS-Short ≤2	Subcohort With ARSSS-Short >2	*P* if <0.1†
N	48	36	12	—
Sex (male/female), n (%)	48 (100)/0	36 (100)/0	12 (100)/0	—
Age, yr (median, interquartile range)	34 (18–69)	35 (25–44)	32 (27–44)	—
Hispanic ethnicity, n (%)	14 (29)	10 (28)	4 (33)	—
Caucasian race, n (%)	25 (52)	19 (53)	6 (50)	—
Asian race, n (%)	3 (6)	2 (6)	1 (8)	—
Black race, n (%)	3 (6)	2 (6)	1 (8)	—
Pacific Islander race, n (%)	3 (6)	3 (8)	0	—
Clinical Characteristics at the Time of Sample Collection	**(median, range)**	**(median, interquartile range)**	**(median, interquartile range)**	***P* if <0.1†**
$CD4^+$ cell count (cells/μL)	465 (120–972)	474 (280–625)	458 (342–555)	—
$CD8^+$ cell count (cells/μL)	602 (91–2831)	545 (269–862)	943 (422–1451)	0.048
$CD4^+/CD8^+$ cell ratio	0.76 (0.13–2.84)	0.92 (0.59–1.24)	0.55 (0.33–0.72)	0.032
Viral load log10 RNA	5.07 (2.53–7.47)	4.12 (3.60–4.86)	5.56 (3.66–6.19)	0.002
Set-point viral load log10 RNA (n = 25)	4.45 (3.32–6.00)	‡	‡	‡
No. signs and symptoms	5 (1–10)	5 (2–6)	7 (5–8)	0.056
Duration of signs and symptoms, d	11 (2–32)	7 (4–12)	14 (11–22)	0.006

*Modification from original score necessary as "inpatient treatment because of signs and symptoms of ARS" was not available.
†*P* value calculated using Mann–Whitney *U* test.
‡Set-point viral load was determined in only 2 patients with ARSSS-short >2. Therefore, results are not displayed.
ALT, alanine aminotransferase; ARS, acute retroviral syndrome; AST, aspartate aminotransferase.

ARS were calculated using Spearman correlation analysis due to the non-normal distributions of ARSSS and laboratory values. The University of California San Diego's Human Research Protections Program approved the study protocol, consent process, and all study-related procedures.

The study cohort composed of 48 participants with AHI. All 48 were men who have sex with men. Characteristics of the study cohort are given in Table 1. The most frequently reported symptom was fever (71%), followed by fatigue (67%), and myalgia (58%).

The cohort had a median ARSSS-short of 1 (range, 0–7; 23% had a score of 0, 48% a score of 1, each 4% a score of 2 and 3, and 21% a score of 4 or above; Table 1). The ARSSS-short was significantly negatively correlated with CD4/CD8 cell ratio (Spearman $\rho = -0.293$; $P = 0.043$) and positively correlated with viral load ($\rho = 0.505$; $P < 0.001$). Significant positive correlations were also observed between the ARSSS-short and number of signs and symptoms of ARS ($\rho = 0.567$; $P < 0.001$) and the total duration of signs and symptoms of ARS ($\rho = 0.398$; $P = 0.007$). No significant correlations were observed between ARSSS-short and CD4 cell count ($\rho = -0.045$; $P > 0.2$) and set point viral load (available in those 25/48 participants who started ART ≥90 days after the Estimated Date of Infection (EDI); $\rho = -0.064$; n.s.). Those with ARSSS-short >2 had significantly lower CD4/CD8 cell ratios, higher viral loads, longer duration of symptoms, and a trend toward more signs and symptoms than those with scores ≤2 (results and *P* values calculated using Mann–Whitney *U* test are depicted in Table 1).

In the 19 individuals with available safety laboratory results, the ARSSS-full (median 1, range 0–8) did not correlate significantly with viral load ($\rho = 0.315$; $P = 0.19$), CD4/CD8 cell ratio ($\rho = 0.037$; $P > 0.2$), or CD4 count ($\rho = -0.039$; $P > 0.2$). Although a significant correlation was observed between ARSSS-full and number of signs and symptoms ($\rho = 0.543$; $P = 0.024$), there was no significant correlation with duration of signs and symptoms ($\rho = 0.300$; $P > 0.2$). Correlations of the ARSSS-short in the subset were as follows: viral loads ($\rho = 0.463$;

$P = 0.046$), CD4/CD8 ratios ($\rho = -0.073$; n.s.), CD4 ($\rho = -0.063$; n.s.), number of signs and symptoms ($\rho = 0.418$; n.s.), and duration of signs and symptoms (0.433; n.s.).

We evaluated the ARSSS, a score to identify individuals with the most severe clinical presentations of ARS who might profit most of immediate ART, among 48 individuals with AHI with an Estimated Date of Infection (EDI) of 10 days at the time of HIV diagnosis. We found that the short version of the score, limited to age and clinical variables that can all be collected at the time of HIV diagnosis, correlated well with severity of ARS in our study cohort, with significant positive correlations between ARSSS-short and viral load, number of ARS signs and symptoms and total duration of signs and symptoms, and a negative correlation between ARSSS-short and CD4/CD8 cell ratios. After being validated in another study, the ARSSS-short may therefore be used to predict diseases severity at the time of HIV diagnosis and therefore significantly earlier than other markers of disease severity. Although immediate ART for all AHI cases is clearly preferable and reflects current recommendations,[1,2] a ARSSS cutoff of >2 may be used for immediate treatment in resource-limited setting, where drug use has to be triaged and is available for only about 25% of AHI cases.

The ARSSS-full (which includes the ARSSS-short variables, plus platelet count and transaminases[18]) could only be evaluated in the subset of participants. Interestingly, integration of laboratory variables into the score in this subset did not improve performance of the score when compared with the ARSSS-short (ie, consisting of clinical variables only). This finding may relate to the small sample size of the subset with safety laboratory results. Previous studies have shown that low platelet count[29,30] and elevated transaminases[31] correlate with HIV-1 disease progression in individuals with recent and chronic HIV infection. However, the prognostic potential of these 2 laboratory values specifically in the earliest stages of HIV infection (ie, Fiebig I and II) has not been evaluated.

In conclusion, the ARSSS-short, which includes 4 easily assessed clinical and demographic variables, may provide a simple and reliable severity score for ARS, and may help identify individuals with the greatest risk of disease progression who would benefit the most from early ART. After validation in another study, the ARSSS-short may therefore help to prioritize treatment in regions where ART is not universally available.

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Sleep Disturbance Among HIV-Infected and Uninfected Veterans

To the Editors:

Although sleep disturbance has been observed at all stages of HIV infection,[1–4] the nature of the association between HIV and sleep disturbance has not been rigorously evaluated in the current treatment era. We explored the longitudinal associations between HIV status and self-reported occurrence or severity of sleep disturbance, with adjustment for demographics, comorbidities, and polypharmacy.

We used the Veterans Aging Cohort Study, a longitudinal prospective observational study of HIV-infected and uninfected Veterans enrolled at 8 Veterans Health Administration (VHA) medical centers: Atlanta, Baltimore, Brooklyn and Manhattan, Bronx, Houston, Los Angeles, Pittsburgh, and Washington DC. HIV-infected Veterans were matched one to one with uninfected Veterans by age, race/ethnicity, site of clinical care, and sex.[5] Data for this analysis included electronic health record data and self-report questionnaires completed by participants at enrollment (baseline) (June 2002 through August 2012) and through 6 years of follow-up.

We defined HIV infection as the presence of *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes for HIV during at least 2 outpatient visits or 1 inpatient event that were confirmed in the immunology case registry of the VHA.[6]

Our primary outcomes were sleep disturbance and its severity. Both were assessed on an annual basis using the self-completed HIV Symptom Index[7] over a follow-up period of 6 years. The index elicits the frequency and severity of discomfort for 20 symptoms commonly associated with HIV. If the symptom was present, participants were prompted to indicate the degree of severity, based on a 5-point Likert scale (0 = does not experience the symptom, 1 = experiences the symptom but without bother, 2 = bothered a little by this symptom, 3 = bothered, and 4 = experiences a lot of bother with the symptom). Sleep disturbance was dichotomized as occurrence (a nonzero response on the Likert scale) or nonoccurrence (a zero response on the Likert scale). Severity was assessed using the ordinal range of responses. Sleep disturbance symptoms were elicited on the survey at baseline and at follow-up visits in years 1–4 and 6, facilitating the longitudinal modeling of sleep disturbance and its severity.

Covariates were selected a priori based on previous sleep disturbance research and data availability. Baseline demographic information included age, sex, and race/ethnicity. All other covariates were updated at each annual assessment. We identified *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes 1 year before and 6 months after baseline for the following conditions: coronary artery disease, diabetes, liver disease (any of hepatitis B or C, cirrhosis, end-stage liver disease), peripheral vascular disease, renal disease, cerebrovascular disease (including stroke), cancer, heart failure, Chronic obstructive pulmonary disease (COPD), other chronic lung diseases, obstructive sleep apnea, Post-traumatic stress syndrome (PTSD), and drug use or abuse.

Body mass index (BMI; weight in kilograms/height in square meter) and pain (pain level between 0 and 10) were identified using vital sign data. We categorized BMI according to World Health Organization criteria: underweight (BMI $<$ 18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (BMI $\geq$ 30). Smoking status was categorized as current, former, and never smoker. From survey data, we used the Patient Health Questionnaire-2 to assess depressive symptoms.[8] Using the Alcohol Use Disorders Identification Test,[9–11] we defined hazardous alcohol use as a score of $\geq$4 for men and $\geq$3 for women. For these time-updated variables, values within 90 days of each survey date were used. If multiple values occurred within this time, the one closest to the survey date was used.

We included a count of unique medications (excluding antiretrovirals) prescribed within 90 days of each survey date over the 6-year follow-up period. Use of selective serotonin reuptake inhibitors (SSRIs), other antidepressants, benzodiazepines, and hazardous opiate use ($\geq$120 morphine equivalents per day) were coded as dichotomous indicator variables. Among HIV-infected individuals, we identified use of antiretroviral therapy (ART) within the same time window and a separate marker of

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